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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,715	07/22/2003	Hans-Peter Beck	UNIBAS0006	4926

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EXAMINER	
SALMON, KATHERINE D	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/623,715	BECK ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *112/29/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *28-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group 1, Claims 1-27 in the reply filed on 12/29/2005 is acknowledged.

2. Claims 28-30 are withdrawn from further consideration.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

4. The use of the trademark SEQUENASE has been noted in this application (paragraph 49, p. 9). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1, 26, and 27 recites the limitation "**a** 3' end" in step A of Claims 1, 26 and 27. There is insufficient antecedent basis for this limitation in the claim. It is unclear it the applicant means the last nucleotide of the 3' end (THE 3' terminal nucleotide) or if the applicant means any nucleotide as long as there is a nucleotide 5' to it.

B. Claim 1 lacks a positive process step relating back to the preamble. The preamble states a method for detecting a single nucleotide polymorphism in a target DNA. The last step recites detecting the presence or absence of hybridized extended primer in the hybridization pattern. Therefore it is unclear whether the method is intended to be drawn to a method of detecting a single nucleotide polymorphism in a target DNA or a method of detecting the presence or absence of hybridized extended primer in the hybridization pattern.

C. Claim 26 lacks a positive process step relating back to the preamble. The preamble states a method for drug resistance testing in malaria. The last step recites

detecting the presence or absence of hybridized extended primer in the hybridization pattern. Therefore it is unclear whether the method is intended to be drawn to a method for drug resistance testing in malaria or a method of detecting the presence or absence of hybridized extended primer in the hybridization pattern.

D. Claims 27 a lacks positive process step relating back to the preamble. The preamble states a method for diagnostic or pharmacogenetic analysis of single nucleotide polymorphisms in a target DNA. The last step recites detecting the presence or absence of hybridized extended primer in the hybridization pattern. Therefore it is unclear whether the method is intended to be drawn to a method for diagnostic or pharmacogenetic analysis of single nucleotide polymorphisms in a target DNA or a method of detecting the presence or absence of hybridized extended primer in the hybridization pattern.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-3, 6-8, 16-23, 25, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Fan et al. (Parallel Genotyping of Human SNPs using generic high-density oligonucleotide tag arrays. June 2000. Genome Research Vol. 10 p. 853).

Fan et al teaches a parallel genotyping method for SNPs that analyzes allele-specific single base extension reactions on standardized, generic high-density oligonucleotide probe arrays (p. 853 1st column last sentence and 2nd column). With regard to Claim 1, 23, and 27, Fan et al. teaches using generic high-density oligonucleotide arrays that contains thousands of preselected 20-mer oligonucleotide tags (Abstract). Fan et al. teaches marker-specific primers are used in PCR amplifications of genomic regions containing SNPs (Abstract). Fan et al. teaches the amplification products are used as templates in single base extension reactions using chimeric primers with 3' complementarily to the specific SNP loci and 5' complementarily to specific probes synthesized on the array (Abstract). Fan et al. teaches the SBE primers, terminating one base before the polymorphic site, are extended in the presences of labeled dideoxy NTPs, using a different label for each of the two SNP alleles, and hybridized to the probe array (Abstract). Fan et al. teaches the genotypes are deduced from the fluorescence intensity ration of the two colors (Abstract).

With regard to Claim 2, Fan et al. teaches the SBE reaction (primer extension) was carried out in multiplex so that products of 9 reactions from each sample were combined (p. 858 Multiplex SBE Reaction).

With regard to Claim 3, Fan et al teaches that genotyping assays for a subset of the total 874 SNPs were identified in a large-scale polymorphism screen of 75 hypertension candidate genes (p. 854 2nd column). Fan et al. teaches 171 SNPs were chosen and PCR primers were designed and tested individually for each of the 173 SNP-containing genomic regions (p. 854 2nd column).

With regard to Claim 6, Fan et al. teaches primers were used at a predicted length of 20 nucleotides (16-26 base pairs) (p. 858 Primer Design). With regard to Claim 7 and 8, Fan et al. teaches a multiplex PCR amplification of the genomic regions containing the 142 SNPs (p. 858 Multiplex PCR). Fan et al. teaches the PCR products were incubated with exonuclease and shrimp alkaline phosphatase to remove residual PCR primers and dNTPs (p. 858 SBE Template Preparation).

With regard to Claims 16 and 17, Fan et al. teaches a multiplex SBE reaction in which fluorescein-N6-d-dNTPs, biotin-N6-d-dUTPs, biotin-N6-d-CTP, and biotin-N6-d-dATP are added to the reaction (p. 858 Multiplex SBE Reaction). With regard to Claim 18 and 25, Fan et al. teaches scanning the arrays on a confocal scanner and fluorescence at 530nm and 560 nm was collected (multilaser scanner) (p. 858 Tag Array Design and Hybridization 3rd paragraph).

With regard to Claims 19-22 and 27, Fan et al. teaches genotyping 44 individuals for 142 SNPs identified previously in 62 candidate hypertension genes (Abstract).

7. Claims 1-3, 7-8, 10, 16-23, 25, and 27 are rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by Huang et al. (US Patent 6,287,778 September 11, 2001).

Huang et al. teaches a method for determining the genotype of one or more individuals at a polymorphic locus employing amplification of a region of DNA, labeling of allele-specific extension primers containing tags, and hybridizing the extension primers to an array of probes (Abstract). With regard to Claim 1, Huang et al. teaches a region of DNA (target DNA) in a sample is amplified using one or a pair of amplification primers to form an amplified DNA product (Column 1, lines 50-66). Huang et al. teaches the region comprises a polymorphic locus (Column 1, lines 50-66). Huang et al. teaches an extension primer is labeled and comprises a 3' portion complementary to the amplified DNA product (Column 1, lines 50-66). Huang et al. teaches the extension primer terminates in a 3' nucleotide at the polymorphic locus of the selected allele (Column 1, lines 50-66). Huang et al. teaches at least one labeled nucleotide is coupled to the 3' terminal nucleotide of the extension primers to form a labeled extension primer (Column 1, lines 50-66). Huang et al. teaches a single base extension reaction in which dideoxynucleotides are attached to the 3' end of the primer (Column 8, lines 58-60). The labeled extension primer is hybridized to a probe on a solid support (Column 1, lines 50-66).

With regard to Claim 2, Huang et al. teaches the reactions of the invention can be performed in a single or multiplex formation (Column 5, lines 54-55). With regard to Claim 3, Huang et al. teaches the size of the region amplified is not critical, but the

region must be sufficiently large to include not only the polymorphic locus but also enough sequence on either side of the polymorphic locus to permit highly specific binding of the primer pairs (Column 7, lines 52-56). To design primers so a region with a polymorphism is amplified, the user of Huang et al.'s method would need to know prior to amplification the location of the SNP. With regard to Claim 7, Huang et al. teaches an allele-specific amplification to amplify the target DNA and then removing excess primers and nucleotides using alkaline phosphatase (Column 8, lines 5-15 and lines 40-45). With regard to Claim 10, Huang et al. teaches the method can be used with various types of DNA including microbial (Column 7, line 1).

With regard to Claim 16, Huang et al. teaches labeling primer extension reactions with fluorescent labels (Column 9, lines 15-22). With regard to Claim 17, Huang et al. teaches using more than one florescent labels (multiple labels) in order to distinguish different alleles at each polymorphic locus (Column 17, lines 55-56). With regard to Claim 18, Huang et al. teaches a confocal microscope can be used with a laser illumination for signal detection (Column 17, lines 39-54). With regard to Claim 25, Huang et al. teaches the emission of fluorescent labels can be detected and measured (fluorochomic quality) (Column 17, lines 55-60).

With regard to Claims 19-22, Huang et al. teaches the amplification step can be performed using up to 300 different primer pairs to amplify a corresponding number of polymorphic sites and theses reactions can be pooled during the primer extension reaction (Column 5, lines 55-60). Huang et al. teaches the method is able to multiplex a

number of different polymorphic loci simultaneously because of the use of sequence tags (Column 5 lines 65-66, and Column 6, lines 1-2).

With regard to Claim 23, Huang et al. teaches high-density arrays can be used to hybridize the target nucleic acid (with a primer extension) to detect the presence of up to more than 1000 allelic markers. The instant specification does not define the limitations of microarray. Microarrays are a type of high-density array, therefore, it is inherent the teaching of Huang et al. encompasses the limitation of the use of a microarray.

With regard to Claim 27, Huang et al. teaches using a clinical sample derived from a patient to determine the relationship between various alleles of a gene and disease (Column 7, lines23-25). Huang et al. teaches the method can be used to detect mutations and to identify the phenotype of mutations (Column 7, lines 23-25).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 4, 5,10-15, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (A mutation-specific PCR system to detect sequence variation in the dihydropteroate synthetase gene of Plasmodium falciparum 1995 Molecular and Biochemical Parasitology. Vol. 71 p. 115) in view of Fan et al. (Parallel Genotyping of Human SNPs using generic high-density oligonucleotide tag arrays. June 2000. Genome Research Vol. 10 p. 853).

Wang et al. teaches a PCR diagnostic assay based on allele-specific amplifications to detect mutations. Wang et al. teaches sulphur-based antimalarial drugs targeted at DHPS are used in combination with inhibitors of DHFR to combat malaria (Abstract). Plasmodium falciparum resistant strains carry point mutations in the DHPS coding region (Claim 3 and 4) (Abstract). Wang et al. teaches the allele specific assays can assess the contribution of specific base changes in the DHPS gene to sulphur drug resistance in malaria (Claim 5) (Abstract). Wang et al. teaches PCR tests for mutations in DHPS would be a powerful, straightforward alternative strategy to monitor sulphadoxine resistance in P. falciparum (Claims 10-15 and 26-27) (p. 116 Introduction last paragraph).

Wang et al. teaches using a nested PCR reaction to amplify target DNA (Claim 7) (p. 117 Polymerase chain reactions). With regard to Claim 1, Wang et al. teaches using the amplified target DNA in a mutation-specific PCR (p. 118 3.1). Wang et al. designed primers that were mismatched to the non-target allele at the 3' end (p. 118 3.1). Wang et al. teaches at each of the 3 mutation positions separate allele-specific primers were designed and the use of specific primers at each site allowed for the multiplexing of the reaction (p.119 1st column last paragraph).

Wang et al. teaches primer length was initially set at or close to 23 nucleotides and adjusted by adding 2-3 nucleotides to the 5' end (primers are between 20-40 nucleotides) (Claim 6). Wang et al. teaches allele-specific methods will allow a rapid and informed expansion of the database of strains that can be usefully tested for linkage between DHPS mutations and in vitro sulphadoxine resistance (p.123 1st column last paragraph).

Wang et al., however, does not teach a method of using mutation-specific PCR system with a flurochrome labeled extended primer hybridized to an array of probes.

Fan et al teaches a parallel genotyping method for SNPs that analyzes allele-specific single base extension reactions on standardized, generic high-density oligonucleotide probe arrays (p. 853 1st column last sentence and 2nd column). With regard to Claim 1, 23, and 27, Fan et al. teaches using generic high-density oligonucleotide arrays that contains thousands of preselected 20-mer oligonucleotide tags (Abstract). Fan et al. teaches marker-specific primers are used in PCR amplifications of genomic regions containing SNPs (Abstract). Fan et al. teaches the

amplification products are used as templates in single base extension reactions using chimeric primers with 3' complementarily to the specific SNP loci and 5' complementarily to specific probes synthesized on the array (Abstract). Fan et al. teaches the SBE primers, terminating one base before the polymorphic site, are extended in the presences of labeled dideoxy NTPs, using a different label for each of the two SNP alleles, and hybridized to the probe array (Abstract). Fan et al. teaches the genotypes are deduced from the fluorescence intensity ration of the two colors (Abstract).

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With regard to Claims 16 and 17, Fan et al. teaches a multiplex SBE reaction in which fluorescein-N6-d-dNTPs, biotin-N6-d-dUTPs, biotin-N6-d-CTP, and biotin-N6-d-dATP are added to the reaction (p. 858 Multiplex SBE Reaction). With regard to Claim 18 and 25, Fan et al. teaches scanning the arrays on a confocal scanner and fluorescence at 530nm and 560 nm was collected (multilaser scanner) (p. 858 Tag Array Design and Hybridization 3rd paragraph).

With regard to Claims 19-22 and 27, Fan et al. teaches genotyping 44 individuals for 142 SNPs identified previously in 62 candidate hypertension genes (Abstract).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Wang et al. to further include using fluorochrome labeled extended primers hybridized to an array of probes. The ordinary artisan would have been motivated improve the method of Wang et al. because Fan et al. teaches a method to analyze thousands of polymorphisms composed of primer extension targets hybridized to a tag array. Fan et al. teaches this method can be customized for sets of markers and is generic, intrinsically parallel, and favors multiplex reactions (p. 853 2nd column). The ordinary artisan would want improve the mutation-specific PCR by increasing the scanning rate by including method steps in which extended primers are hybridized to an array of probes so thousands of samples to determine drug-resistance in malaria samples can be analyzed simultaneously.

10. Claims 1-8 and 10-23 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (A mutation-specific PCR system to detect sequence

variation in the dihydropteroate synthetase gene of Plasmodium falciparum 1995 Molecular and Biochemical Parasitology. Vol. 71 p. 115) in view of Huang et al. (US Patent 6,287,778 September 11, 2001).

Wang et al. teaches a PCR diagnostic assay based on allele-specific amplifications to detect mutations. Wang et al. teaches sulphur-based antimalarial drugs targeted at DHPS are used in combination with inhibitors of DHFR to combat malaria (Abstract). Plasmodium falciparum resistant strains carry point mutations in the DHPS coding region (Claim 3 and 4) (Abstract). Wang et al. teaches the allele specific assays can assess the contribution of specific base changes in the DHPS gene to sulphur drug resistance in malaria (Claim 5) (Abstract). Wang et al. teaches PCR tests for mutations in DHPS would be a powerful, straightforward alternative strategy to monitor sulphadoxine resistance in P. falciparum (Claims 10-15 and 26-27) (p. 116 Introduction last paragraph).

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Wang et al., however, does not teach a method of using mutation-specific PCR system with a flurochrome labeled extended primer hybridized to an array of probes.

Huang et al. teaches a method for determining the genotype of one or more individuals at a polymorphic locus employing amplification of a region of DNA, labeling of allele-specific extension primers containing tags, and hybridizing the extension primers to an array of probes (Abstract). With regard to Claim 1, Huang et al. teaches a region of DNA (target DNA) in a sample is amplified using one or a pair of amplification primers to form an amplified DNA product (Column 1, lines 50-66). Huang et al. teaches the region comprises a polymorphic locus (Column 1, lines 50-66). Huang et al. teaches an extension primer is labeled and comprises a 3' portion complementary to the amplified DNA product (Column 1, lines 50-66). Huang et al. teaches the extension primer terminates in a 3' nucleotide at the polymorphic locus of the selected allele (Column 1, lines 50-66). Huang et al. teaches at least one labeled nucleotide is coupled to the 3' terminal nucleotide of the extension primers to form a labeled extension primer (Column 1, lines 50-66). Huang et al. teaches a single base extension reaction in which dideoxynucleotides are attached to the 3' end of the primer (Column 8, lines 58-60). The labeled extension primer is hybridized to a probe on a solid support (Column 1, lines 50-66).

With regard to Claim 2, Huang et al. teaches the reactions of the invention can be performed in a single or multiplex formation (Column 5, lines 54-55). With regard to Claim 3, Huang et al. teaches the size of the region amplified is not critical, but the region must be sufficiently large to include not only the polymorphic locus but also enough sequence on either side of the polymorphic locus to permit highly specific binding of the primer pairs (Column 7, lines 52-56). To design primers so a region with a polymorphism is amplified, the user of Huang et al.'s method would need to know prior to amplification the location of the SNP. With regard to Claim 7, Huang et al. teaches an allele-specific amplification to amplify the target DNA and then removing excess primers and nucleotides using alkaline phosphatase (Column 8, lines 5-15 and lines 40-45). With regard to Claim 10, Huang et al. teaches the method can be used with various types of DNA including microbial (Column 7, line 1).

With regard to Claim 16, Huang et al. teaches labeling primer extension reactions with fluorescent labels (Column 9, lines 15-22). With regard to Claim 17, Huang et al. teaches using more than one florescent label (multiple labels) in order to distinguish different alleles at each polymorphic locus (Column 17, lines 55-56). With regard to Claim 18, Huang et al. teaches a confocal microscope can be used with a laser illumination for signal detection (Column 17, lines 39-54). With regard to Claim 25, Huang et al. teaches the emission of fluorescent labels can be detected and measured (fluorochomic quality) (Column 17, lines 55-60).

With regard to Claims 19-22, Huang et al. teaches the amplification step can be performed using up to 300 different primer pairs to amplify a corresponding number of

polymorphic sites and theses reactions can be pooled during the primer extension reaction (Column 5, lines 55-60). Huang et al. teaches the method is able to multiplex a number of different polymorphic loci simultaneously because of the use of sequence tags (Column 5 lines 65-66, and Column 6, lines 1-2).

With regard to Claim 23, Huang et al. teaches high-density arrays can be used to hybridize the target nucleic acid (with a primer extension) to detect the presence of up to more than 1000 allelic markers.

With regard to Claim 27, Huang et al. teaches using a clinical sample derived from a patient to determine the relationship between various alleles of a gene and disease (Column 7, lines23-25). Huang et al. teaches the method can be used to detect mutations and to identify the phenotype of mutations (Column 7, lines 23-25).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Wang et al. to further include using fluorochrome labeled extended primers hybridized to an array of probes. The ordinary artisan would have been motivated improve the method of Wang et al. because Huang et al. teaches a method for obtaining genotype information on thousands of polymorphisms in a highly parallel fashion in order to map disease loci and identify quantitative trait loci, thereby, simultaneously evaluating large numbers of genetic polymorphisms (Column 1, lines 10-15 and 17-18). The ordinary artisan would want improve the mutation-specific PCR by increasing the scanning rate by including method steps in which extended primers are hybridized to an array of probes so

thousands of samples to determine drug-resistance in malaria samples can be analyzed simultaneously.

11. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al. (US Patent 6,287,778 September 11, 2001) in view of Zammatteo et al. (Comparison between different strategies of covalent attachment of DNA to glass surfaces to build DNA microarrays. 2000, Analytical Biochemistry. Vol. 280 p. 143).

Huang et al. teaches a method for determining the genotype of one or more individuals at a polymorphic locus employing amplification of a region of DNA, labeling of allele-specific extension primers containing tags, and hybridizing the extension primers to an array of probes (Abstract). With regard to Claim 1, Huang et al. teaches a region of DNA (target DNA) in a sample is amplified using one or a pair of amplification primers to form an amplified DNA product (Column 1, lines 50-66). Huang et al. teaches the region comprises a polymorphic locus (Column 1, lines 50-66). Huang et al. teaches an extension primer is labeled and comprises a 3' portion complementary to the amplified DNA product (Column 1, lines 50-66). Huang et al. teaches the extension primer terminates in a 3' nucleotide at the polymorphic locus of the selected allele (Column 1, lines 50-66). Huang et al. teaches at least one labeled nucleotide is coupled to the 3' terminal nucleotide of the extension primers to form a labeled extension primer (Column 1, lines 50-66). Huang et al. teaches a single base extension reaction in which dideoxynucleotides are attached to the 3' end of the primer (Column 8, lines 58-60). The labeled extension primer is hybridized to a probe on a solid support (Column 1,

lines 50-66). With regard to Claim 23, Huang et al. teaches high-density arrays can be used to hybridize the target nucleic acid (with a primer extension) to detect the presence of up to more than 1000 allelic markers.

Huang et al., however, does not teach the use of an aldehyde slide or immobilizing the probes on the slide with a C6 amino linker.

Zammatteo et al. teaches various types of slides for microarray analysis and a description of the linking of probes to an array. Zammatteo et al. teaches the efficiency of a DNA microarray depends mainly on the sequence of the capture probes and the way the probes are attached to the support (Abstract). Zammatteo et al. teaches a fixation of aminated DNA to an aldehyde-modified surface is one of the preferred methods to build DNA microarrays (Abstract). Zammatteo et al. teaches preparing aldehyde-covered microscope slides by transforming the terminal ester groups of TETU into aldehyde groups on a glass slide (p. 144 Amino-silane modification). Zammatteo et al. teaches the attachment of the 5' end of DNA to glass supports using a 6-carboxy linker (Figure 1 part 3 p. 146).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Huang et al. to use an aldehyde slide with probes attached with a linker as taught by Zammatteo et al. The ordinary artisan would have been motivated to use aldehyde slides because Zammatteo et al. teaches that aldehyde is a preferred coating for microarray slides because nonspecific binding is not observed and DNA probes are fixed specifically (Results 2nd column p. 146). Mishybridization would occur between the probe and the extended

primer if the probes on the array were not specifically fixed, therefore, a method without aldehyde coated slides would have a higher error rate in determining the genotypes of bound DNA than a method with aldehyde coated slides.

12. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fan et al. (Parallel Genotyping of Human SNPs using generic high-density oligonucleotide tag arrays. June 2000. Genome Research Vol. 10 p. 853) in view of Zammatteo et al. (Comparison between different strategies of covalent attachment of DNA to glass surfaces to build DNA microarrays. 2000, Analytical Biochemistry. Vol. 280 p. 143).

Fan et al teaches a parallel genotyping method for SNPs that analyzes allele-specific single base extension reactions on standardized, generic high-density oligonucleotide probe arrays (p. 853 1st column last sentence and 2nd column). Fan et al. teaches using generic high-density oligonucleotide arrays that contains thousands of preselected 20-mer oligonucleotide tags (Abstract). Fan et al. teaches marker-specific primers are used in PCR amplifications of genomic regions containing SNPs (Abstract). Fan et al. teaches the amplified products are used as templates in single base extension reactions using chimeric primers with 3' complementarily to the specific SNP loci and 5' complementarily to specific probes synthesized on the array (Abstract). Fan et al. teaches the SBE primers, terminating one base before the polymorphic site, are extended in the presences of labeled dideoxy NTPs, using a different label for each of the two SNP alleles, and hybridized to the probe array (Abstract). Fan et al. teaches the

genotypes are deduced from the fluorescence intensity ration of the two colors (Abstract).

Fan et al., however, does not using aldehyde microarray slides.

Zammatteo et al. teaches various types of slides for microarray analysis and a description of the linking of probes to an array. Zammatteo et al. teaches the efficiency of a DNA microarray depends mainly on the sequence of the capture probes and the way the probes are attached to the support (Abstract). Zammatteo et al. teaches a fixation of aminated DNA to an aldehyde-modified surface is one of the preferred methods to build DNA microarrays (Abstract). Zammatteo et al. teaches preparing aldehyde-covered microscope slides by transforming the terminal ester groups of TETU into aldehyde groups on a glass slide (p. 144 Amino-silane modification). Zammatteo et al. teaches the attachment of the 5' end of DNA to glass supports using a 6-carboxy linker (Figure 1 part 3 p. 146).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Fan et al. to use an aldehyde slide with probes attached with a linker as taught by Zammatteo et al. The ordinary artisan would have been motivated to use aldehyde slides because Zammatteo et al. teaches that aldehyde is a preferred coating for microarray slides because nonspecific binding is not observed and DNA probes are fixed specifically (Results 2nd column p. 146). Mishybridization would occur between the probe and the extended primer if the probes on the array were not specifically fixed, therefore, a method without

aldehyde coated slides would have a higher error rate in determining the genotypes of bound DNA than a method with aldehyde coated slides.

13. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al. (US Patent 6,287,778 September 11, 2001) in view of Hodson et al. (In situ PCR for visualization of microscale distribution of specific genes and gene products in prokaryotic communities. Nov. 1995. Applied and environmental microbiology. p. 4074).

Huang et al. teaches a method for determining the genotype of one or more individuals at a polymorphic locus employing amplification of a region of DNA, labeling of allele-specific extension primers containing tags, and hybridizing the extension primers to an array of probes (Abstract). With regard to Claim 1, Huang et al. teaches a region of DNA (target DNA) in a sample is amplified using one or a pair of amplification primers to form an amplified DNA product (Column 1, lines 50-66). Huang et al. teaches the region comprises a polymorphic locus (Column 1, lines 50-66). Huang et al. teaches an extension primer is labeled and comprises a 3' portion complementary to the amplified DNA product (Column 1, lines 50-66). Huang et al. teaches the extension primer terminates in a 3' nucleotide at the polymorphic locus of the selected allele (Column 1, lines 50-66). Huang et al. teaches at least one labeled nucleotide is coupled to the 3' terminal nucleotide of the extension primers to form a labeled extension primer (Column 1, lines 50-66). Huang et al. teaches a single base extension reaction in which dideoxynucleotides are attached to the 3' end of the primer (Column 8, lines 58-60).

The labeled extension primer is hybridized to a probe on a solid support (Column 1, lines 50-66).

With regard to Claim 7, Huang et al. teaches an allele-specific amplification to amplify the target DNA and then removing excess primers and nucleotides using alkaline phosphatase (Column 8, lines 5-15 and lines 40-45).

Huang et al., however, does not teach performing the allele-specific amplification as an in situ PCR.

Hodson et al. teaches a method for prokaryotic in situ PCR where single cells within complex mixtures can be identified and characterized genetically (Abstract). Hodson et al. teaches a method involving amplification of specific nucleic acid sequences inside intact prokaryotic cells followed by color or fluorescence detection of the localized PCR product (Abstract).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Huang et al. to perform an in situ allele specific PCR. The ordinary artisan would have been motivated to improve the method of Huang et al. by using a in situ method for PCR amplification of the target DNA because Hodson et al. teaches the use of in situ PCR protocol allows information on the actual numbers, microscale patchiness, and physical associations of bacterial cells (p. 4079 Discussion). The ordinary artisan would want to use the in situ PCR method in order to get information on specific genes and gene products at the individual cell level (p. 4080 1st paragraph).

14. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Fan et al. (Parallel Genotyping of Human SNPs using generic high-density oligonucleotide tag arrays. June 2000. Genome Research Vol. 10 p. 853) in view of Hodson et al. (In situ PCR for visualization of microscale distribution of specific genes and gene products in prokaryotic communities. Nov. 1995. Applied and environmental microbiology. p. 4074).

Fan et al teaches a parallel genotyping method for SNPs that analyzes allele-specific single base extension reactions on standardized, generic high-density oligonucleotide probe arrays (p. 853 1st column last sentence and 2nd column). Fan et al. teaches using generic high-density oligonucleotide arrays that contains thousands of preselected 20-mer oligonucleotide tags (Abstract). Fan et al. teaches marker-specific primers are used in PCR amplifications of genomic regions containing SNPs (Abstract). Fan et al. teaches the amplification products are used as templates in single base extension reactions using chimeric primers with 3' complementarily to the specific SNP loci and 5' complementarily to specific probes synthesized on the array (Abstract). Fan et al. teaches the SBE primers, terminating one base before the polymorphic site, are extended in the presences of labeled dideoxy NTPs, using a different label for each of the two SNP alleles, and hybridized to the probe array (Abstract). Fan et al. teaches the genotypes are deduced from the fluorescence intensity ration of the two colors (Abstract).

Fan et al., however, does not teach performing the marker-specific amplification as an in situ PCR.

Hodson et al. teaches a method for prokaryotic in situ PCR where single cells within complex mixtures can be identified and characterized genetically (Abstract). Hodson et al. teaches a method involving amplification of specific nucleic acid sequences inside intact prokaryotic cells followed by color or fluorescence detection of the localized PCR product (Abstract).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Fan et al. to perform an in situ marker specific PCR. The ordinary artisan would have been motivated to improve the method of Huang et al. by using a in situ method for PCR amplification of the target DNA because Hodson et al. teaches the use of in situ PCR protocol allows information on the actual numbers, microscale patchiness, and physical associations of bacterial cells (p. 4079 Discussion). The ordinary artisan would want to use the in situ PCR method in order to get information on specific genes and gene products at the individual cell level (p. 4080 1st paragraph).

Conclusion

15. No Claims allowed over the cited prior art.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Katherine Salmon 1/19/2006

Katherine Salmon
Examiner
Art Unit 1634

Jehanne Sitton

JEHANNE SITTON
PRIMARY EXAMINER

1/20/06